III. Remarks

A. Status of the Claims

As an initial matter, Applicant acknowledges with appreciation the entry of the amendment dated October 2, 2009, and the Examiner's conclusion that claims 15, 16 and 18 are allowed. Applicant acknowledges that the amendment after final filed on June 21, 2010 was not entered for the alleged reasons of record.

Claims 1-3, 5, 7-16, 18 and 19 were pending in this application, and claims 1-3, 5, 7-14, and 19 have been rejected. Claims 15, 16 and 18 have been allowed.

Claims 12-15 will be amended upon entry of this amendment.

Claims 1-3, 5, 7-11 and 19 will be canceled upon entry of this amendment.

Claims 21 and 22 will be added upon entry of this amendment.

Claims 4, 6, 17 and 20 were *previously canceled.*

Claim 12 has been amended by the **addition** of:

the phrase --immunoglobulin G-- in front of "~~first~~ an ionic protein";

the term, --protein-- in front of "sample" in step (a);

the phrase --immunoglobulin G-- after "sample";

the term --different-- after "second";

the phrase --consisting of protein A-- after "compound";

the phrase --consisting of agarose beads having sulphopropyl groups attached thereto and-- after the term "adsorbent";

the phrase --(b) ionically binding the immunoglobulin G to the agarose beads having sulphopropyl groups attached thereto--;

--(c)-- in front of "washing";

the phrase --agarose beads having sulphopropyl groups attached thereto-- after "washing the ~~cation-exchange adsorbent~~";

the phrase -- protein A-- in after "unbound";

--(d)-- in front of "applying";

the phrase --agarose beads having sulphopropyl groups attached thereto-- after "washing the ~~cation-exchange adsorbent~~";

--(e)-- in front of "eluting";

the phrase --immunoglobulin G-- after bound; and

the phrase --agarose beads having sulphopropyl groups attached thereto-- after "washing the ~~cation-exchange adsorbent~~.

Claim 12 has been amended by the **deletion** of:

the term "first" in front of the phrase "ionic protein" at each occurrence;

the phrases, in step (b), "wherein the ionic charge density of the cation-exchange adsorbent is selected such that", and "first ionic protein compound of interest binds to the cation-exchange adsorbent and the second different ionic protein compound is unbound to the cation-exchange adsorbent";

the phrases, in step (c), "cation-exchange adsorbent", and "second different ionic protein compound";

the phrase, in step (d), "cation-exchange adsorbent"; and

the phrases, in step (e), "first ionic protein compound of interest" and "cation-exchange adsorbent".

Claim 13 has been amended by the **addition** of: the term --selective-- in front of "cation-exchange adsorbent", and the phrase --consisting of agarose beads having sulphopropyl groups attached thereto-- after "cation-exchange adsorbent". Support for these amendments are found in the specification as originally filed, at least in para [0026]; and in Example 1.

Claim 14 has been amended by the **addition** of: the term --selective-- in front of "cation-exchange adsorbent", and the phrase --consisting of agarose beads having sulphopropyl groups attached thereto-- after "cation-exchange adsorbent". Support for these amendments are found in the specification as originally filed at least in para [0026]; and in Example 1.

Claim 15 has been amended by the **addition** of the phrase --sulphopropyl groups attached thereto" after the phrase "adsorbent having". Support for this amendment is found in the specification as originally filed at least in para [0026]; and in Example 1.

New claim 21, dependent upon allowed claim 15, has been added wherein the ionic charge density is claimed from 30 to 80 μmol/ml. Support for this amendment is found in the specification as originally filed at least in para [0012].

New claim 22, dependent upon allowed claim 15, has been added wherein the selective cation-exchange adsorbent comprises agarose beads. Support for this amendment is found in the specification as originally filed at least in para [0026]; and in Example 1.

The foregoing claim amendments were made solely in an effort to expedite prosecution and allowance of the present application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Applicant believes that *no new matter has been added* to the claims by these amendments.

Applicant acknowledges with appreciation the Examiner's withdrawal of the following objections/rejections:

i.) The objection to claim 6 under 37 CFR 1.75, since claim 6 has been cancelled.

ii.) The rejection of claims 1 and 5 under 35 USC 112, 2nd paragraph allegedly for inconsistent recitations.

iii.) The rejection of claim(s) 1, 12 and 15 under 35 USC §112, 2nd paragraph, for the recitation of the now deleted phrase, "in the absence of an added salt...".

iv.) The rejection of claims 1-3 and 5-20 under 35 USC §112, 1st paragraph, for the recitation of the now deleted phrase, "in the absence of an added salt...".

v.) The rejection of claims 1-3 and 5-20 under 35 USC §112, 1st paragraph, allegedly for failure to disclose the best mode, because Applicant has provided a conductivity range for the buffer used in Example 1 that would permit one to calculate the permissible range and/or upper limit of concentration for a positive charged ion that bind to the adsorbent.

vi.) The rejection of claim 20 under 35 USC §112, 1st paragraph, for allegedly adding new matter, since claim 20 has been cancelled.

vii.) The rejection of claims 19-20 under 35 USC §112, 1st paragraph, regarding the alleged lack of enablement for binding "only the selected ionic polymeric compound".

viii.) The rejection of claim 19 has been overcome, due to changes introduced into base claim 15.

ix.) The prior art rejection of claims 12 and 15-16 based upon *Scholz et al.*, since each of claims 12 and 15 recite an ionic charge density range, and *Scholz* fails to teach the ligand density of any of the adsorbents studied. There is thus no standard reference which one could consult in order to determine what might be the inherent ligand density of any of the adsorbents.

x.) The prior art rejection of claims 15-17 and 19 based upon *Lihme et al.* which fails to teach separating protein A from IgG.

xi.) The prior art rejection of claims 15-16 based upon *Hahn et al.* which fails to teach separating protein A from IgG.

xii.) The 102/103 rejection of claims 1, 5-6, 9-12 and 15-16 based upon *Reithorst et al.* which fails to teach cation exchangers.

xiii.) The prior art rejection of claims 15-19 based upon *Graf et al.* which fails to teach separating protein A from IgG.

Accordingly, upon entry of the present amendment and response, claims 12 to 16, 18, 21 and 22 will be pending.

B. Claim Objections

The Office Action objected to claim 2 under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office Action objected to claim 9 under 37 CFR 1.75(i), as being of improper format for failing to indent step c).

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this objection and solely in an effort to expedite prosecution and allowance of the pending claims, claims 2 and 9 will be canceled upon entry of this amendment, rendering these objections moot.

C. 35 U.S.C. §112 second paragraph rejections

12, second paragraph, and resp The Office Action rejected claims 1-3, 5 and 7-14 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons:

In claim 1, line 10 "the cation-exchange adsorbent" allegedly lacks antecedent basis, because claim 1 recites a "selective cation-exchange adsorbent".

In claim 1, last line "the selective ionic adsorbent" allegedly lacks antecedent basis, because claim 1 recites a "selective cation-exchange adsorbent".

In claim 2, "the selective ionic adsorbent" allegedly lacks antecedent basis, because base claim 1 recites a "selective cation-exchange adsorbent".

In claim 5, line 3 and in claims 10-11, line 2 of each claim, "the selective cation-exchange ionic adsorbent" allegedly lacks antecedent basis, because base claim 1 recites a "selective cation-exchange adsorbent".

Claim 12, at lines 3 and 7, refers to a "selective cation-exchange adsorbent" and subsequently refers to "the cation exchange adsorbent". Dependent claims 13-14 also refer to "the cation exchange adsorbent". The Office Action asserts that consistent terminology is required.

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection, and solely in an effort to expedite prosecution and allowance of the pending claims, Applicant has, upon entry of this amendment:

i.) canceled claims 1-3 and 5-11, rendering the rejection of these claims moot; and

ii.) amended claims 12, 13 and 14 by inserting the term --selective-- in front of the phrase "cation-exchange adsorbent", and inserting the phrase --consisting of agarose beads having sulphopropyl groups attached thereto-- after "cation-exchange adsorbent".

Applicant submits that claims 12 to 14 meet the specific requirements of 35 U.S.C. §1ectfully requests reconsideration and withdrawal of this rejection.

D. 35 U.S.C. §112 first paragraph rejections

1. Claim 19 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action asserts that:

> "Claim 19 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. *Applicant has not described a "sample component" in accord with the limitations of claim 19.*
>
> Specifically, base claim 15 has been amended such that the sample is one containing a "protein-A component" and an "IgG component". Applicant has not described how a "protein-A component" would be one normally found in a blood sample or cell culture broth..."

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection and solely in an effort to expedite prosecution and allowance of the pending claims, upon entry of this amendment, claim 19 will be canceled, thereby rendering this rejection moot.

E. 35 U.S.C. §102 REJECTION

1. Claims 1-2 and 9-11 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by *Wu et al.*, "Effects of Stationary Phase Ligand Density On High-performance Ion-exchange Chromatography of Proteins", Journal of Chromatography 598, 7-13, 1992, (hereinafter referred to as "*Wu*"). The Office Action alleges that *Wu* teaches experiments in which protein solutions, in a buffer of 0.01 M (10 mM) sodium phosphate are prepared, and each of these protein solutions are contacted with a series of carboxylate cation-exchangers/adsorbents having different carboxylate ion (ligand) densities, such that the proteins are adsorbed to each of the

exchangers. At a carboxylate ligand density of 70 umol/g the exchanger/adsorbent starts to become saturated with protein (e.g. lysozyme). See pgs 8-10 and Fig. 2.

The Office Action asserts that instant claims 1 and 2 are anticipated in that in claim 1, a protein binds to the cation exchange adsorbent and thereby separate the protein from a "sample component". The Office Action interprets the "sample component" to be merely the solution of the individual protein in 10 mM sodium phosphate buffer since Applicant uses the phrase "sample component" to refer to an even more complex mixture containing the ionic protein component of interest.

The Office Action alleges that *Wu* elutes the adsorbed protein from each of these cation exchangers, by varying sodium sulfate concentration in the 10 mM sodium phosphate buffer (See Fig. 4); thus the Office Action concludes claim 9 is anticipated.

The Office Action acknowledges that Applicant's arguments filed 10/2/09 have been fully considered but they are not persuasive. Furthermore, the Office Action alleges that salt from a buffer can be present in/added to the sample, since Applicant's teachings in Example 1 include the addition of a buffer to the sample.

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection and solely in an effort to expedite prosecution and allowance of the pending claims, upon entry of this amendment claims 1-2 and 9-11 will be canceled, thereby rendering this rejection moot.

2. Claims 1-2, 5, 7 and 9-14 are rejected under 35 U.S.C. §102(a), (b) or (e) as being anticipated by *Lihme et al.* (US 6,498,236 or WO 98/08603), hereinafter referred to as "*Lihme*". The US and foreign references have the same disclosure. The rejection is based upon §102 (a)/(e) for the former and under 102 (b) for the latter. *For convenience, the Office Action refers to the U.S. document by col. and line number.*

The Office Action alleges that:

> "*Lihme* teaches chromatographic adsorbents/matrices which have a negative charge on their surface, due to the presence of a COOH group attached to an aromatic ring. This group would be ionized at the taught pK range values for the COOH group and the taught pH ranges values for adsorption (e.g. see col. 8, lines 46-65, and col. 15, lines 25-41)...For the exemplified 2-mercapto-nicotinic acid, the pH values at which binding of immunoglobulins occurs are in the acid range, where the COOH group would be ionized (e.g. col. 36, lines 1-50). The operative and exemplified ligand densities are taught at col. 18, lines 17-32; col. 30, lines 29-34; col. 34, lines 62-67; col. 35, lines 62-65; col. 38, line 31; and col. 39, line 39. The exemplified separations of IgG from an "Artificial Culture Supernatant" (col. 30, lines 30+) and from sera (col. 38, lines 9+) show a separation in which a "first ionic

> protein compound of interest" in a sample binds to the adsorbent and a "second different ionic protein compound" (e.g. one or more proteins in the fetal calf serum of the "Artificial Culture Supernatant") in a sample do not bind to the adsorbent, as in instant claim 12. This exemplification is also consistent with the case in which a "selected ionic protein compound of interest" binds to the adsorbent and a "sample component"...does not bind to the adsorbent, as in instant claim 1...claim 9, note that *Lihme* elutes the adsorbed IgG.

The Office Action acknowledges that Applicant's arguments filed 10/2/09 have been considered, but found the arguments not persuasive.

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection and solely in an effort to expedite prosecution and allowance of the pending claims, upon entry of this amendment claims 1-2, 5, 7 and 9-11 will be canceled, thereby rendering this rejection moot as it pertains to those claims. Upon entry of this amendment claims 12-14 will be amended. Claim 12 is amended in part as follows:

> "A method of separating IgG...from a protein sample...using a selective cation-exchange adsorbent having a sufficiently low ionic charge density to ionically bind to the ionic protein compound of interest, comprising the steps of: (a) contacting a protein sample <u>containing IgG</u> *and* <u>protein A</u>, with a selective cation-exchange adsorbent consisting of agarose beads having sulphopropyl groups...(b) ionically binding IgG to the agarose beads...(c) washing the agarose beads...<u>to remove unbound protein A</u>; (d) applying a salt gradient of increasing conductivity to the agarose beads...(e) eluting the ionically bound IgG from the agarose beads...".

Lihme teaches a method for the isolation or purification of IgG from a solution. The method includes the use of salts in the binding process, and small amounts of organic solvents in the elution process. The solid phase matrices, preferably epichlorohydrin activated agarose, are functionalised with mono/bicyclic aromatic or heteroaromatic ligands (molecular weight: at the most 500 Dalton) which, preferably, comprises an acidic substituent, e.g. a carboxylic acid.

Applicant respectfully contends that *Lihme* fails to teach each of the elements in claims 12-14. For example, *Lihme* at least fails to teach or anticipate (a) contacting a sample having <u>both IgG **and** protein A</u> with a cation-exchange adsorbent; (b) ionically binding IgG to the adsorbent; and (c) washing the adsorbent to <u>remove unbound protein A</u>. As such, Applicant respectfully contends that the anticipatory rejection over *Lihme* has been rebutted, and respectfully requests reconsideration and withdrawal of this rejection.

3. Claims 12 to 14 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by *Hahn*

et al. (Jour. Chromat. A., 795, 277-287, 1998), (hereinafter referred to as "*Hahn*").

The Office Action contends that *Hahn* teaches a sample of bovine whey prepared by the addition of HCL to milk in order to precipitate casein, which is then removed by centrifugation. The obtained whey is diluted with water to a conductivity of 2.7 mS/cm. The Office Action contends that such preparation of whey is indistinguishable from that exemplified by Applicant (Example 2). See *Hahn* at pp. 278-279. The whey is then contacted with a cation-exchange resin, including S-Sepharose FF (p. 278, col. 2), under conditions such that IgG binds to the adsorbent and alpha-lactalbumin passes through the column (pp. 280-281). The Office Action concludes *Hahn* teaches a separation in which a "first ionic protein compound of interest" in a sample binds to the adsorbent, and a "second different ionic protein compound" in a sample does not bind to the adsorbent.

The Office Action admits that *Hahn* does not teach the charge density of the Sepharose employed, but nonetheless concludes that it must have been the same as or close to that having a charge density of 75 umol/ml as taught by Applicant in Example 2. The Office Action assumes that otherwise, there would have been no selective binding of the IgG, hence, claims 12-14 are anticipated or, at the least, obvious over *Hahn*.

The Office Action acknowledges that Applicant's arguments filed 10/2/09 have been fully considered but are not persuasive. The Office Action acknowledges that while Applicant has urged (p. 15) that *Hahn* does not meet all the limitations recited in claim 12, the Office considers that the charge density of the Sepharose employed by *Hahn* must have been the same as or close to the charge density of 75 umol/ml exemplified by applicant in Example 2, since *Hahn* and applicant both differentially adsorbed whey proteins to the Sepharose.

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection and solely in an effort to expedite prosecution and allowance of the pending claims, and upon entry of this amendment, claims 12 to 14 have been amended.

Applicant respectfully contends that *Hahn* fails to teach all of the elements in claims 12 to 14. For example, *Hahn* at least fails to teach or anticipate (a) contacting a sample having both IgG **and** protein A with a cation-exchange adsorbent; (b) ionically binding IgG to the adsorbent; and (c) washing the adsorbent to remove unbound protein A. As such, Applicant respectfully contends that the anticipatory rejection over *Hahn* has been rebutted, and respectfully requests reconsideration and withdrawal of this rejection.

4. Claims 1-2, 5, 7, 9 and 12 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over *Graf et al.* (Bioseparation, 4, 7-20, 1994), (hereinafter referred to as "*Graf*"). The Office Action contends that *Graf* teaches various ion exchange matrices/adsorbents for the separation of a MAb from an animal cell culture fluid, and asserts that the ueq/ml values given in Table correspond to the umol/ml values recited in the

instant claims. SP Sepherodex M has a binding capacity of 100 ueq/ml (upper end of range recited in instant claims 1 and 12). The Office Action contends using a cation exchanger, the majority of the MAbs present in the animal cell culture fluid sample binds to the exemplified columns, and "most of the contaminant proteins are removed in the flow through fraction" (pg. 12, col. 2). The Office Action thus concludes there is selective binding of MAbs to the matrices/adsorbents. Regarding claim 9, the Office Action contends *Graf* elutes the adsorbed antibody (pg. 12, col. 1-2). The Office Action considers that the claims are anticipated; however, an obviousness rejection is made in the alternative.

Applicant respectfully traverses this rejection.

Without acquiescing to the validity of this rejection and solely in an effort to expedite prosecution and allowance of the pending claims, upon entry of this amendment claims 1-2, 5, 7 and 9 will be canceled, thereby rendering this rejection moot.

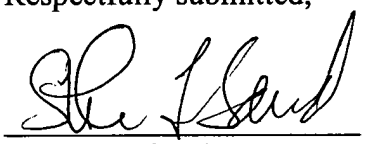
Graf teaches that the productivity in MAb purification processes may be improved by varying the flow rate, the sample concentration, and the size of the chromatography column. In addition, *Graf* also teaches optimizing buffer conditions (ph and ionic strength) and choice of cation exchangers to further improve MAb chromatographic purification. In *Graf*, MAbs from different starting materials such as ascitic fluid and animal cell cultures are chromatographically purified in a single step (pg. 18, col. 1) using a 20 mM MES buffer, under pH 6.50 adsorption conditions, and a cation-exchanger to achieve at least 90% purity of the MAb, wherein cation-exchange supports, such as S Sepharose FF, exhibit a higher capacity for MAb purification compared to anion exchangers.

However, Applicant respectfully contends that *Graf* fails to teach all of the elements in claim 12. For example, *Graf* at least fails to teach or anticipate as claimed in claim 12, (a) contacting a sample having **both IgG** and **protein A** with a cation-exchange adsorbent; (b) ionically binding IgG to the adsorbent; and (c) washing the adsorbent to remove unbound protein A. Applicant respectfully contends that the anticipatory rejection over *Graf* has been rebutted, and respectfully requests reconsideration and withdrawal of this rejection.

IV. Conclusion

In view of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of the rejections, and the timely allowance of the pending claims. Applicant believes that the above response is a complete response to the present Office Action. If however the Examiner believes that some requirement has been missed or not completely answered, the Examiner is invited to contact Applicant's attorney at the number below. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account.

Respectfully submitted,



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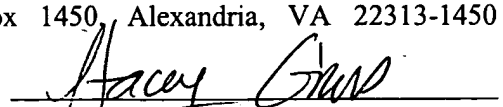

Stacey Gross